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ORIGINAL PAPER

Survival loss linked to guideline-based indications for degenerative mitral regurgitation surgery

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Aims

Operating on patients with severe degenerative mitral regurgitation (DMR) is based on ACC/AHA or ESC/EACTS guidelines. Doubts persist on best surgical indications and their potential association with postoperative survival loss. We sought to investigate whether guideline-based indications lead to late postoperative survival loss in DMR patients.

Methods and results

We analysed outcome of 2833 patients from the Mitral Regurgitation International Database registry undergoing surgical correction of DMR. Patients were stratified by surgical indications: Class I trigger (symptoms, left ventricular end-systolic diameter ≥ 40 mm, or left ventricular ejection fraction < 60%, $n = 1677$), isolated Class IIa trigger [atrial fibrillation (AF), pulmonary hypertension (PH), or left atrial diameter ≥ 55 mm, $n = 568$], or no trigger ($n = 588$). Postoperative survival was compared after matching for clinical differences. Restricted mean survival time (RMST) was analysed. During a median 8.5-year follow-up, 603 deaths occurred. Long-term postoperative survival was lower with Class I trigger than in Class IIa trigger and no trigger (71.4 ± 1.9, 84.3 ± 2.3, and 88.9 ± 1.9% at 10 years, $P < 0.001$). Having at least one Class I criterion led to excess mortality ($P < 0.001$), while several Class I criteria conferred additional death risk [hazard ratio (HR): 1.53, 95% confidence interval (CI): 1.42–1.66]. Isolated Class IIa triggers conferred an excess mortality risk vs. those without (HR: 1.46, 95% CI: 1.00–2.13, $P = 0.05$). Among these patients, isolated PH led to decreased postoperative survival vs. those without (83.7 ± 2.8% vs. 89.3 ± 1.6%, $P = 0.011$), with the same pattern observed for AF (81.8 ± 5.0% vs. 88.3 ± 1.5%, $P = 0.023$). According to RMST analysis, compare to those operated on without triggers, operating on Class I trigger patients led to 9.4-month survival loss ($P < 0.001$) and operating on isolated Class IIa trigger patients displayed 4.9-month survival loss ($P = 0.001$) after 10 years.

Conclusion

Waiting for the onset of Class I or isolated Class IIa triggers before operating on DMR patients is associated with postoperative survival loss. These data encourage an early surgical strategy.

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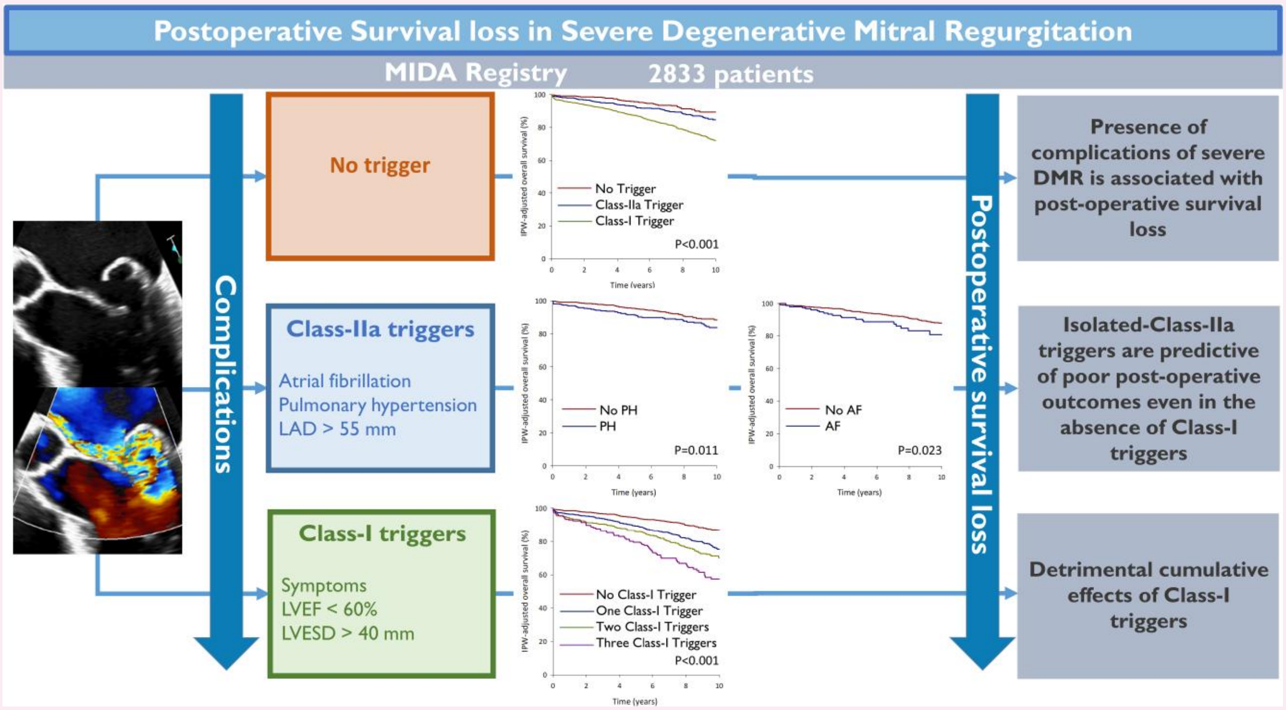
Graphical Abstract



AF, atrial fibrillation; DMR, degenerative mitral regurgitation; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; PH, pulmonary hypertension.

Keywords degenerative mitral regurgitation • survival loss • inverse probability weighting • prognosis • international registry

Introduction

Valvular heart disease (VHD) represents an essential public health problem, affecting >2.2% of the general population, with degenerative mitral regurgitation (DMR) as the most common VHD in western countries.[1,2] DMR is a progressive disease, which is associated with significant morbidity and mortality when not timely treated.[3] Haemodynamic consequences of DMR, including left atrial and left ventricular (LV) enlargement and dysfunction, pulmonary hypertension (PH), atrial fibrillation (AF), and the symptoms of heart failure, complicate variably the clinical course of DMR patients[4–7] and justify taking the risk of surgical correction of DMR. Therefore, based on this perception of the clinical risk/benefit balance, American[8] and European[9] clinical guidelines have for many years placed the most stringent trigger for surgery (i.e. Class I) as onset of symptoms or presence of LV systolic dysfunction [LV ejection fraction (LVEF) ≤ 60% or LV end-systolic diameter (LVESD) ≥ 40 mm]. The ESC/EACTS guidelines recommend intervention as a Class IIa indication for patients with AF, systolic pulmonary arterial pressure (SPAP) > 50 mmHg, or left atrial diameter (LAD) ≥ 55 mm, whereas the AHA/ACC guidelines no longer base their recommendations on these criteria. Instead, the AHA/ACC guidelines state that operating on asymptomatic patients proves reasonable in the absence of Class I criteria in case of a high probability of durable repair (Class IIa indication). In the absence of large randomized studies, current recommendations are mainly based on registry data. Among registry patients with DMR, performance of early mitral surgery compared with initial medical management was indeed proven associated with improved long-term survival.[10,11]

Despite these recommendations, the current management of patients with significant DMR is too often conservative, with numerous patients not being referred to surgery.[2,12] Surgery is partly underused because some practitioners consider valve replacement surgery to be associated with high mortality and reoperation rates. However, in the majority of tertiary centres, DMR surgery consists of a valve repair that is associated with very low operative mortality (<0.5%) and excellent durability (freedom from reoperation at 15 years >93%).[13] Such improvements in surgical techniques have opened the way to earlier interventions. Nevertheless, whether long-term postsurgical outcome, in the era of valve repair and low operative risk, proves to be similar, irrespective of surgical triggers (Class I or Class IIa), or whether it is impacted by these triggers is still unclear and understudied.[14,15] Thus, it is essential to analyse long-term outcomes based on the triggers that led to surgery, as it could impact guideline content drafting and, as such, DMR undertreatment. Accordingly, in this work, we sought to explore the impact of guideline criteria on postoperative patient survival rates. Therefore, we analysed patients from the Mitral Regurgitation International Database (MIDA) registry and we sought to test the hypothesis that waiting for Class I or IIa guideline criteria to occur before operating on patients with severe DMR would be associated with a postoperative survival loss.

Methods

Study design

The MIDA registry has systematically merged consecutive experiences with mitral regurgitation due to flail mitral valve (MV) leaflets of nine tertiary centres. Of these, two were in France, three in Italy, one in Belgium, one in the USA, one in Singapore, and one in Hong Kong (see Supplementary data online, *Appendix S1*—MIDA investigators). The process of forming each centre's data set involved retrospective identification of consecutive patients diagnosed with DMR based on echocardiography. Echocardiographic variables were obtained via downloading standardized measurements, which were prospectively entered into the databases. All participating medical centres provided ethics and institutional review board approvals for this study. The study was conducted in accordance with institutional policies and national legal requirements prevailing at the time of patient recruitment.

Eligibility

Patients were enrolled into the MIDA registry if they had DMR with a flail leaflet detected using 2D echocardiography from 1980 to 2018.[10] Specific eligibility criteria to participate in our study were as follows: (i) echocardiographically diagnosed severe DMR; (ii) availability of a comprehensive clinical/instrumental evaluation at the time of baseline echocardiography; (iii) exclusion of ischaemic MR attributable to previous or ongoing myocardial infarction; and (iv) absence of significant concomitant aortic valve disease, congenital diseases, mitral stenosis, or prior valve surgery. For the current analysis, we considered only surgically treated patients. Indication for surgery relied on shared decision-making by the patient, cardiologist, and cardiac surgeon. Patients were stratified according to surgical indication into three different groups: Class I trigger group (symptoms, LVESD $\geq$ 40 mm, or LVEF < 60%), isolated Class IIa trigger group (AF, PH, or LAD $\geq$55 mm without any Class I trigger), or no trigger group (none of the above).

Echocardiography

As previously published, transthoracic echocardiograms were performed within routine clinical practice, using standard methods at the time of patient's inclusion.[10] LV dimensions were assessed from parasternal long-axis views using 2D direct measurements or guided M-mode echocardiography at end-diastole and end-systole. Ejection fraction was calculated using ventricular dimensions. Diagnosis of flail leaflet was based on failure of leaflet coaptation, with rapid systolic movement of the involved leaflet tip within the left atrium. The use of an integrated approach to establish the severity of valvular lesions was in line with the recommendations provided by the guidelines. Since the MIDA registry focuses on routine clinical practice, echocardiographic data were analysed as collected at the time of echocardiography performed without subsequent modification or central review.

Baseline evaluation, outcomes, and follow-up

The patient clinical characteristics at baseline, as reported into the MIDA registry, were those collected by personal physicians at the time of echocardiography. These data were reported unaltered. Patients were followed-up by their personal physicians within each participating centre or outside. Information on follow-up events was obtained by direct patient interviews and clinical examinations or by repeated follow-up letters and questionnaires. Documentation of testing and surgical reports were reviewed and validated by the investigators. The primary endpoint was postoperative survival.

Statistical analysis

Continuous variables were expressed as mean $\pm$ SD and compared by using the two-sided Student's *t*-test or Wilcoxon rank sum test as appropriate. Categorical variables were expressed as frequency percentages and analysed using χ^2 tests. Follow-up times were expressed as median and interquartile range (IQR). Overall survival was computed using the Kaplan–Meier methodology, with comparisons carried out using log-rank χ^2 tests. Cox proportional hazard models assessed hazard ratios (HRs) and 95% confidence intervals (CIs) relating to surgical indication groups. We employed univariable models and multivariable models adjusting for age, obstructive coronary disease, diabetes, hypertension, flail type, chronic kidney disease, chronic pulmonary disease, surgery type (replacement or repair), and associated coronary artery bypass graft surgery (CABG). In order to obtain comparable patient cohorts by weighing individual patients according to mismatched characteristics, we computed inverse probability weights (IPWs) from predicted probabilities of trigger class assignment (Class I trigger, Class IIa trigger, and no trigger). Briefly, propensity scores for trigger class assignment were first computed using a 1:1:1 multinomial logistic regression model, with the response variable being 'no trigger' class (0, used as reference), Class IIa trigger (1), and Class I trigger (2). The covariables employed to build the propensity scores included age, Asian origin, obstructive coronary disease, diabetes, hypertension, flail type, chronic kidney disease, chronic pulmonary disease, surgery type (replacement or repair), and associated CABG. Using the propensity scores, a case–weight estimation was performed in order to predict the inverse probability of being in a given trigger class category. The IPW weight was then employed within the Cox proportional hazard regression model to generate a weighted population with a balanced distribution of covariables for unbiased estimates of death hazard associated with the different trigger class groups. Variables employed to construct indication groups (symptoms, LVEF, LVESD, LAD, AF, and PH) were not adjusted so as to avoid tautological inferences. The proportional hazard assumption within the Cox models was assessed with Schoenfeld residuals, while the model fit was evaluated using martingale and Cox–Snell residuals. Finally, survival loss was quantified according to surgical indication (Class I trigger vs. Class IIa trigger vs. no trigger) using restricted mean survival time (RMST) analysis at the truncated time point of 10 years.[16] All statistical analyses were conducted using the R software 4.0.3 (IPW, weights packages, and survRM2 packages) and SPSS Version 20.0 (IBM Inc.; Chicago, IL). A *P*-value of <0.05 was considered statistically significant.

Results

Baseline characteristics

Overall, 3977 patients were enrolled in the MIDA registry (*Figure 1*). The final population of patients eligible for our study consisted of 2833 patients, 1677 (59%) of whom presenting with Class I triggers, 568 (20%) with isolated Class IIa triggers (in the absence of Class I trigger), and 588 (21%) with no trigger. Baseline characteristics were stratified by trigger class groups and by weighing approaches (*Table 1*). After IPW, the differences in age and comorbidities were no longer statistically significant among groups. MV surgery was performed within 9.8 $\pm$ 23.3 months of diagnosis (median, 1.41 months). For immediate (30 days) postoperative outcomes, the observed mortality was 1.8, 1, and 0.3% for patients operated on with Class I trigger, Class IIa trigger,

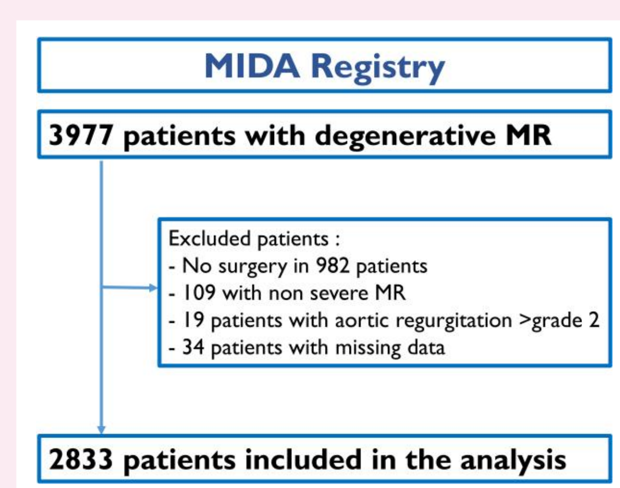


Figure 1 Study population. Flowchart detailing the identification of the study population.

Table 1 Baseline characteristics by trigger class group

	Overall population					IPW population				
	No trigger group ($n = 588$)	Class IIa trigger group ($n = 568$)	Class I trigger group ($n = 1677$)	SMD	*P*-value	No trigger group ($n = 588$)	Class IIa trigger group ($n = 568$)	Class I trigger group ($n = 1677$)	SMD	*P*-value
Non–trigger-related characteristics										
Age (years)	60 ± 13	62 ± 12	65 ± 12	**0.253**	**<0.001**	63 ± 12	63 ± 12	63 ± 13	0.016	0.93
Male (%)	74.5	74.1	72.7	0.026	0.65	73	73.5	73.3	0.004	0.99
Renal insufficiency (%)	2.2	2.8	3.2	0.039	0.49	2.3	2.7	2.9	0.011	0.79
Chronic pulmonary disease (%)	5.1	7.9	9	**0.102**	**0.011**	8.4	7.9	8	0.026	0.96
History of CAD (%)	16.8	14.3	19.9	**0.100**	**0.007**	16.6	18	17.8	0.026	0.76
Hypertension (%)	35.4	39.4	42.9	**0.103**	**0.005**	39.7	40.7	40.6	0.009	0.93
Diabetes (%)	4.4	6.9	8.6	**0.113**	**0.003**	5.8	7.6	7.4	0.030	0.39
Flail anterior (%)	10.7	11.6	14.5	0.076	**0.024**	13.4	13	13.2	0.016	0.98
Flail posterior (%)	82	81.9	77.7	0.071	**0.024**	79.2	79.6	79.4	0.016	0.98
Associated CABG (%)	11.9	13.4	18.2	**0.119**	**<0.001**	15.8	16	15.9	0.014	>0.99
MV repair (%)	95.2	91	90.2	**0.130**	**0.001**	91.4	91.6	91.4	0.005	0.99
Trigger-related characteristics										
Symptoms (%)	0	0	46.1	**0.872**	**<0.001**	0	0	43.8	**0.676**	**<0.001**
LVEF (%)	67 ± 5	69 ± 6	61 ± 10	**0.651**	**<0.001**	67.5 ± 5	69 ± 5.5	61 ± 10	**0.538**	**<0.001**
LVEF < 60% (%)	0	0	38.8	**0.751**	**<0.001**	0	0	38.7	**0.616**	**<0.001**
LVESD (mm)	33 ± 4	33 ± 4	38 ± 8	**0.558**	**<0.001**	33 ± 4	33 ± 4	38 ± 8	**0.517**	**<0.001**
LVESD >40 mm (%)	0	0	44.5	**0.844**	**<0.001**	0	0	44.8	**0.679**	**<0.001**
Atrial fibrillation (%)	0	26.4	24.7	**0.565**	**<0.001**	0	26.9	24.5	**0.462**	**<0.001**
LAD (mm)	44 ± 6	52 ± 9	51 ± 10	**0.627**	**<0.001**	45 ± 6	52 ± 10	51 ± 10	**0.529**	**<0.001**
LAD >55 mm (%)	0	40.1	35.7	**0.768**	**<0.001**	0	40.8	33.8	**0.592**	**<0.001**
PH (SPAP at rest > 50 mmHg; %)	0	59.5	48.5	**1.103**	**<0.001**	0	58.9	46.2	**0.799**	**<0.001**

Bold values indicate statistically significant differences.
CABG, coronary artery bypass graft; CAD, coronary artery disease; IPW, inverse probability weight; MV, mitral valve; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; PH, pulmonary hypertension; SMD, standardized mean difference; SPAP, systolic pulmonary arterial pressure.

Table 2 IPW-adjusted Cox regression analysis for all-cause mortality

Cox regression analysis	Univariate		Multivariate	
	HR 95% (CI)	*P*-value	HR 95% CI	*P*-value
Non–trigger-related characteristics				
Age (year)	1.09 (1.08–1.10)	**<0.001**	1.08 (1.07–1.09)	**<0.001**
Male gender	0.91 (0.77–1.09)	0.36	1.13 (0.94–1.35)	0.21
Geographical origin	0.54 (036–0.79)	**0.003**	1.00 (0.67–1.50)	>0.99
Renal insufficiency	2.23 (1.53–3.27)	**<0.001**	1.56 (1.05–2.3)	**0.026**
Chronic pulmonary disease	20 (1.57–2.55)	**<0.001**	1.27 (0.98–1.65)	0.070
History of CAD	1.88 (1.56–2.26)	**<0.001**	1.14 (0.93–1.40)	0.22
Hypertension	1.42 (1.21–1.67)	**<0.001**	1.01 (0.85–1.20)	0.92
Diabetes	1.94 (1.5–2.5)	**<0.001**	1.42 (1.09–1.84)	**0.009**
Anterior flail leaflet	1.55 (1.26–1.91)	**<0.001**	1.49 (1.2–1.85)	**<0.001**
Posterior flail leaflet	0.74 (0.62–0.89)	**0.002**	0.97 (0.70–1.35)	0.86
MV repair	0.42 (0.35–0.52)	**0.001**	0.56 (0.45–0.69)	**0.001**
Associated CABG	1.72 (1.43–2.07)	**<0.001**	1.24 (1.02–1.51)	**0.028**
Trigger-related characteristics				
Symptoms	2.19 (1.87–2.57)	**<0.001**	1.19 (1.08–1.3)	**<0.001**
LVEF <60% (%)	1.54 (1.29–1.84)	**<0.001**	1.27 (1.04–1.54)	**0.018**
LVESD >40 mm (%)	1.4 (1.18–1.66)	**0.001**	1.24 (1.02–1.49)	**0.027**
Atrial fibrillation	2.13 (1.8–2.53)	**<0.001**	1.3 (1.08–1.56)	**0.005**
LAD >55 mm	1.51 (1.29–1.78)	**<0.001**	1.23 (1.04–1.46)	**0.015**
PH (SPAP at rest > 50 mmHg)	1.66 (1.41–1.96)	**<0.001**	1.2 (1.01–1.43)	**0.041**

Bold values indicate statistically significant differences.
CABG, coronary artery bypass graft; CAD, coronary artery disease; IPW, inverse probability weight; MV, mitral valve; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; PH, pulmonary hypertension; SPAP, systolic pulmonary arterial pressure.

and no trigger, respectively ($P = 0.025$). Furthermore, there were 117 reinterventions [12/588 (2.0%) in the no trigger group, 21/568 (3.7%) in the isolated Class IIa trigger group, and 84/1677 (5.0%) in the Class I trigger group ($P = 0.007$)]. Interestingly, there was a clear trend towards operating on patients at an earlier time in their disease stage, with patients operated on without triggers becoming more common, while patients with Class I triggers were less commonly operated on with time (see Supplementary data online, *Table S1*). We found no effect of time on the guideline criteria (*P* for interaction for AF: 0.9, for PH: 0.17, and for LAD: 0.88).

Predictors of postoperative survival in the entire population

During a median 8.5-year (IQR: 5.9–11.6) follow-up, 603 deaths occurred. Survival in the entire cohort at 5 and 10 years was 90.0 ± 0.6 and $77.1 \pm 1.2\%$, respectively. Not surprisingly, according to univariable Cox regression analysis, age, comorbidities, flail type, MV repair, and associated CABG were predictors of mortality, as were Class I or Class IIa guideline triggers. In IPW-adjusted multivariable Cox regression analysis, age, renal insufficiency, diabetes, and Class I or Class IIa guideline triggers turned out to be predictors of mortality (*Table 2*).

Impact of Class I triggers on postoperative survival

We tested the impact of individual Class I triggers on postoperative survival (*Figure 2*). In the entire population, the 10-year overall postoperative survival was significantly higher in asymptomatic patients ($82.2 \pm 1.3\%$) than in those exhibiting symptoms ($65.2 \pm 3.0\%$, $P < 0.001$). These differences persisted following IPW adjustment (*Figure 2A*). Moreover, the 10-year overall postoperative survival was also significantly better in patients with a preoperative LVEF > 60% than in those displaying a preoperative LVEF < 60% ($79.3 \pm 1.4\%$ vs. $69.9 \pm 3.2\%$, $P < 0.001$). These differences persisted after IPW adjustment (*Figure 2B*). In addition, the 10-year overall postoperative survival was significantly better among patients with preoperative LVESD <40 mm than in those with a preoperative LVESD > 40 mm ($79.2 \pm 1.4\%$ vs. $71.9 \pm 2.7\%$, $P = 0.024$). These differences persisted after IPW adjustment as well (*Figure 2C*). Additionally, we analysed the cumulative effect of Class I triggers on overall mortality. Patients were stratified according to the presence of none, one, two, or three Class I triggers, whatsoever the trigger (*Figure 3*). There was a strong impact of Class I triggers on postoperative survival compared to those patients without any Class I trigger (no Class I trigger vs. one Class I trigger, $P < 0.001$; one Class I trigger vs. two Class I triggers, $P = 0.027$; two Class I triggers vs. three Class I triggers, $P = 0.004$). Moreover, having multiple Class I triggers was associated with a cumulative risk of mortality [HR: 1.53 (1.42; 1.66), $P < 0.001$]. To test the hypothesis that there is a gradient of risk according to the severity of Class I triggers, spline curves centred on Class I triggers (LVEF and LVESD) were constructed (see Supplementary data). As anticipated, the spline curves indicated a progressive increase in mortality risk as the trigger thresholds were approached, the risk for patients beginning to rise when the LVEF was below 65% (see Supplementary data online, *Figure S1*) or when the LVESD exceeded 40 mm (see Supplementary data online, *Figure S2*).

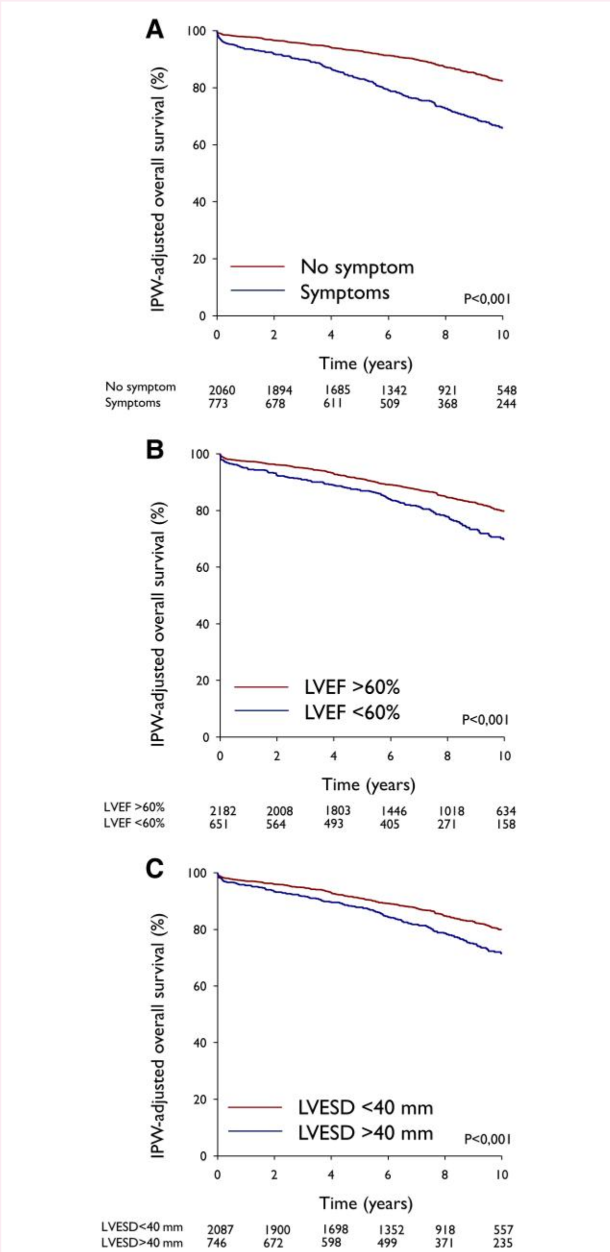


Figure 2 IPW-adjusted overall postoperative survival stratified according to the presence of Class I triggers. Ten-year overall postoperative survival was significantly higher in asymptomatic patients than in those exhibiting symptoms (*A*), better in patients with a preoperative LVEF > 60% than in those displaying a preoperative LVEF < 60% (*B*), and better among patients with preoperative LVESD < 40 mm than in those with a preoperative LVESD > 40 mm (*C*). IPW, inverse probability weight.

Postoperative survival according to guideline trigger classes

The 10-year overall postoperative survival of patients operated on without triggers was better vs. those operated on for either isolated Class IIa or Class I triggers (88.9 ± 1.9, 84.3 ± 2.3, and 71.4 ± 1.9%, respectively, $P < 0.001$). Similar results were observed following IPW adjustment (90.0 ± 1.8, 85.2 ± 2.1, and 71.4 ± 1.9%, respectively, $P < 0.001$, *Figure 4*). To test the ability of guideline triggers to predict overall postoperative survival, we constructed preliminary multivariable Cox proportional models for which all preoperative clinical variables were proposed for inclusion. The ability of trigger classes to improve the prediction of death by these preliminary models was then tested. Class I triggers including symptomatic status (χ^2 test to enter: 19.5, $P < 0.001$), LVEF < 60% (χ^2 test to enter: 15.2, $P < 0.001$), and LVESD >40 mm (χ^2 test to enter: 13.5, $P < 0.001$) enabled an improved prediction of overall postoperative survival. Similarly, Class IIa triggers, including PH (χ^2 test to enter: 7.68, $P = 0.006$), AF (χ^2 test to enter: 11.6, $P < 0.001$), and LAD >55 mm (χ^2 test to enter: 15.0, $P < 0.001$) permitted an improved prediction of postoperative overall survival.

Impact of isolated Class IIa triggers on postoperative survival in the absence of Class I triggers

We conducted an analysis on Class IIa criteria patients without any Class I criteria to evaluate the specific impact of isolated Class IIa triggers on postoperative survival. Among these patients operated on without any Class I trigger, having an isolated Class IIa trigger conferred an excess mortality risk compared to those without any trigger (HR: 1.46, 95% CI: 1.00–2.13, $P = 0.050$). Isolated PH was associated with decreased postoperative survival vs. those without any PH (89.3 ± 1.6% vs. 83.7 ± 2.8%, $P = 0.011$, *Figure 5A*). We observed the same pattern for isolated AF (88.3 ± 1.5% vs. 81.8 ± 5.0%, $P = 0.023$, *Figure 5B*), while LAD alone did not confer a survival loss at 10 years (89.0 ± 1.4% vs. 81.9 ± 4.1%, $P = 0.16$, *Figure 5C*).

RMST analysis

RMST analysis was performed on the IPW-adjusted population (*Figure 6*). A mean survival loss was estimated at 10 years following mitral surgery by comparing groups according to the presence of guideline triggers. After 10 years, when compared with patients operated on without any guideline triggers, operating on Class I trigger patients was associated with an estimated mean survival loss of 9.4 months [RMST difference in months: −9.38 (−12.05; −6.70), $P < 0.001$], and operating on Class IIa trigger patients was associated with an estimated mean survival loss of 4.9 months [RMST-difference in months: −4.86 (−7.78; −1.95), $P = 0.001$].

Discussion

The current work examines postoperative outcomes of DMR from the MIDA registry according to guideline-based triggered surgery. The current analysis indicates (*Graphical Abstract*) the following:

(1) The presence of a Class I guideline trigger (symptoms, LVEF < 60%, or LVESD > 40 mm) at the time of surgery in patients with severe DMR appears to be deleterious, being accompanied by an increased mortality risk compared to those without any trigger (about 20–30% more risk of postoperative death vs. no trigger at 10 years).
(2) There is a detrimental cumulative effect (up to 50% more risk) of Class I triggers on postoperative survival.
(3) In the absence of any Class I trigger, an isolated Class IIa trigger like AF or PH is accompanied by decreased postoperative survival, as well, resulting in an undeniable survival loss compared to those without any trigger.

Controversy regarding the timing of surgical correction for severe DMR still exists despite compelling data establishing a better outcome in patients operated on at an earlier time compared to those for whom a watchful waiting strategy is being adopted. Although active surveillance in a strict framework was associated with equivalent outcomes in asymptomatic patients with severe DMR,[17] numerous studies

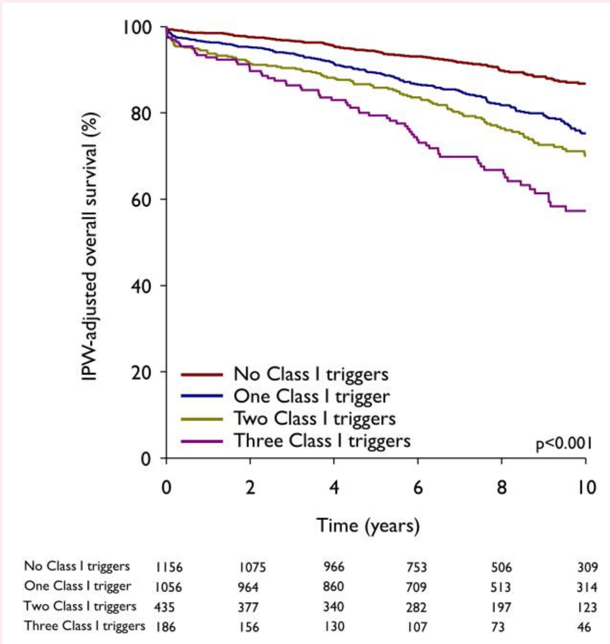


Figure 3 IPW-adjusted overall postoperative survival stratified according to the presence and the number of Class I triggers. There was a strong impact and a cumulative effect of Class I criteria on postoperative survival compared to those patients without any Class I trigger.

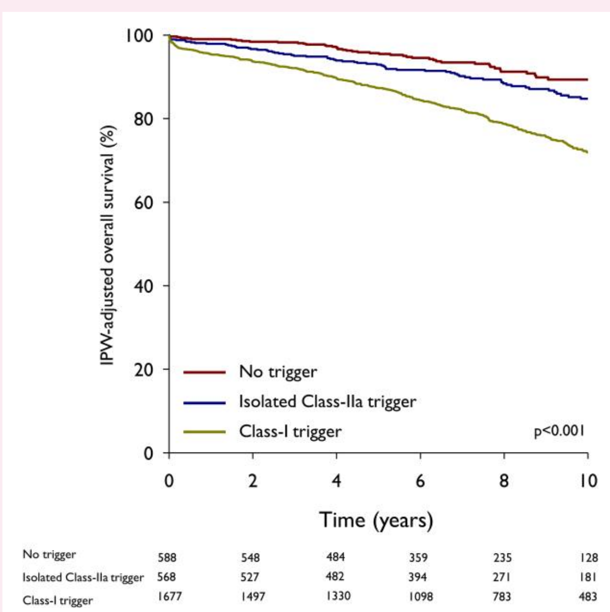


Figure 4 IPW-adjusted overall postoperative survival stratified according to guideline trigger classes. Ten-year overall postoperative survival of patients operated on without triggers was better vs. those operated on for either isolated Class IIa or Class I triggers.

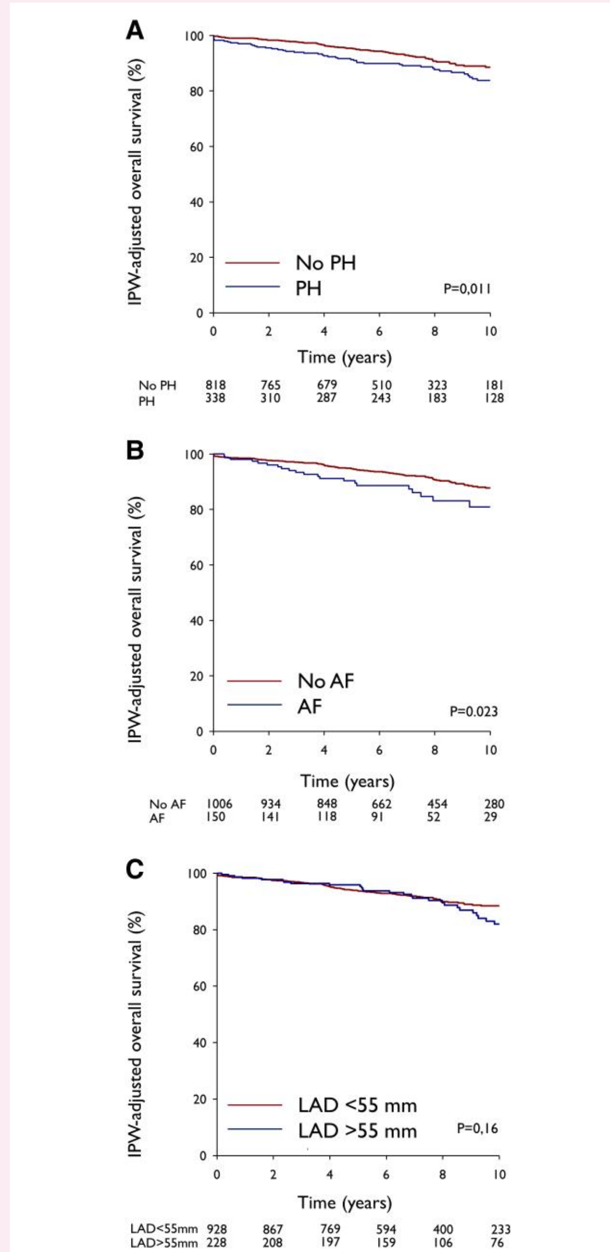


Figure 5 IPW-adjusted overall postoperative survival stratified according to Class IIa triggers in the absence of Class I triggers. Isolated PH was associated with decreased postoperative survival vs. those without any PH (*A*). We observed the same pattern for isolated AF (*B*), while LAD alone did not confer a survival loss at 10 years (*C*). AF, atrial fibrillation; LAD, left atrial diameter; PH, pulmonary hypertension.

performed involving larger patient groups have established an enlarged ventricle (LVESD > 40 mm), LVEF < 60%, PH, and AF[4–6] exert definite consequences on survival of patients for whom follow-up is being 'offered' as first-line strategy compared to those who undergo surgery at an earlier time point. While these data on the natural disease history represent already a strong argument for proposing early surgical treatment, our work exclusively focused on postoperative survival further reinforces the message that waiting does not constitute an acceptable attitude. The current guideline triggers lead to rescue surgery when these triggers are present at the time of surgery. Given the survival loss related to these triggers, the optimal surgical timing must actually be prior to the onset of these triggers.

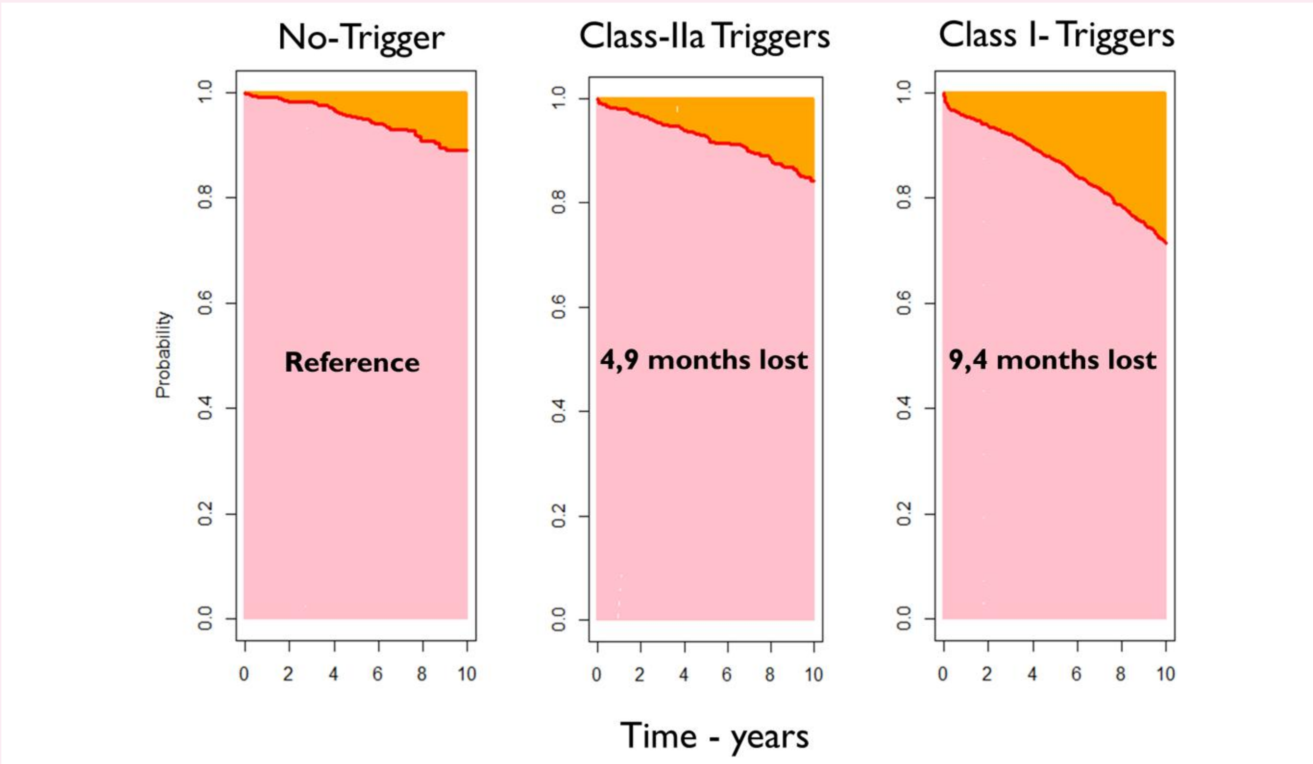


Figure 6 IPW-adjusted restricted mean survival time at 10 years. Waiting for Class I trigger onset was associated with a long-term survival loss of 9.4 months, while waiting for Class IIa trigger onset was associated with a long-term survival loss of 4.9 months when compared to patients without any trigger.

Implications of current Class I trigger guidelines on outcome

Class I triggers used to indicate surgery for severe DMR are linked to worse long-term postoperative outcomes. This observation is obtained by accounting for identified confounders and using multiple methods that clearly demonstrated that the impact of Class I triggers on post-operative outcomes was unadulterated and independent. All Class I triggers were associated with reduced survival, consistent with other series.[13,14,18] Our analysis demonstrated better survival in asymptomatic patients compared to symptomatic ones. Several authors consider mitral repair for Class I-designated patients, as suggested by the American guidelines, to be a good approach, whereas interventions at the earliest symptom onset likewise yield excellent results.[13] Given the late survival loss linked to patients exhibiting symptoms, as shown in this work, along with the unpredictable symptomatic evolution of severe DMR, surgery should be proposed to asymptomatic patients before that potential irreversible LV complications do occur.[19] Considering the low referral rates to surgery of patients with Class I triggers, there is still a long way to go, with a clear need to further improve guideline implementation.[2,12]

Class IIa triggers are not a 'licence to wait'

This work is the first to focus on Class IIa trigger patients and this, in the absence of any Class I triggers. One key finding is that, even in the absence of symptoms or LV dysfunction/dilatation, Class IIa triggers (AF and PH) impact long-term mortality, except isolated LAD > 55 mm. Enlarged LAD is associated with a worse natural history in a DMR population, whereas its impact on postoperative survival is likely less pronounced, except for patients with a very large LA volume >60 mL/m^2.[7] By applying the strict criterion of 55 mm as suggested by the current guidelines, we found no negative outcome for asymptomatic patients with isolated LAD. The occurrence of LV dysfunction, symptoms (Class I triggers), and the occurrence of AF and PH (Class IIa triggers) were shown to worsen the late postoperative prognosis of DMR. The American guidelines[8] state that careful monitoring may result in mitral surgery timing before these negative sequelae occur, whereas these recommendations also present early mitral repair (Class IIa indication, before reaching Class I triggers) as an attractive alternative. Indeed, early mitral repair avoids the need for intensive surveillance, which is not always easy to implement. Our data further support this therapeutic strategy since all complications related to DMR (symptoms, LVEF < 60%, LVESD >40 mm, AF, or PH > 50 mmHg) are associated with poorer postoperative outcomes compared to patients being operated on without any complication. From our point of view, all complications related to DMR should be considered as equal as there is no evidence indicating a trigger hierarchy. Indeed, our data indicate that the risk associated with each complication is similar, for both Class I and Class IIa criteria (20–30% additional risk whatever the complication). Furthermore, the presence of Class I triggers at the time of surgery was associated in our analysis with higher perioperative mortality, as already demonstrated in other studies.[14,18] This is an additional argument to not defer surgery until Class I triggers become apparent, unless operative risk is high and repair probability turn out to be poor. This strategy is acceptable if surgery is performed safely in high-volume centres.[20,21] A recent study indicates AF, PH, LAD, and moderate to severe tricuspid regurgitation affect postoperative survival in all DMR severity ranges.[15] Our data obtained in patients with flail leaflet reinforce this message.

Limitations of the study

Despite the prospective nature of the MIDA registry and the completeness of our follow-up data, our study lacks randomization between early surgery and active surveillance, potentially introducing unaccounted confounding factors. In this work, we could not evaluate the IIb indication according to the American guidelines[8]; these latter state that asymptomatic patients with a progressively reduced ejection fraction or progressively increased LV diameter could be considered for surgery. Our results are specific to patients with flail MV leaflets and may not be generalized to other MV disease aetiologies. Data on MV repair failure or MR recurrence rates were unavailable. Lastly, we were not able to provide data regarding LA volume, LV global longitudinal strain, natriuretic peptides, or the impact of surgical AF ablation on outcomes, although these parameters could undoubtedly help to refine the selection of patients eligible for surgery.

Conclusion

Waiting for the onset of Class I or Class IIa-triggers before operating on patients with severe DMR is associated with a definite postoperative survival loss as compared with patients operated on without any trigger being present. Furthermore, there is a detrimental cumulative effect related to Class I triggers. Therefore, the absence of guideline triggers should not be interpreted as a 'licence to wait'. These data should encourage all clinicians to adopt an early surgical strategy in severe DMR patients for whom a repair can be offered. Early surgery performed in good-expertise (high repair rates) and high-volume (low operative risk) centres should be the preferred strategy for severe DMR patients to avoid postoperative long-term survival loss. The American guidelines propose a Class IIa indication to operate on asymptomatic patients if the probability of repair is high and the expected operative risk is <1%. Our data support this statement.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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Data availability

The data underlying this article will be shared upon reasonable request to the corresponding author.

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